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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/801,729
Filing Date: March 15, 2004
Appellant(s): Kao et al.

Kao et al.
For Appellant

EXAMINER'S ANSWER

This is in response to the Appellant's Appeal Brief filed January 11, 2008.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief contains a statement concerning related appeals or interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct

This appeal involves claims 1, 3-8, 10, 12-13, 19-24, 30, 32-33, 37 and 39.

(4) Status of Amendments

The statement of the status of amendments contained in the brief is correct. The Appellant's amendments after final to claims 3, 23, 33 and 37 have been filed and entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to Be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Appendix

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

WO 00/56403 A1	LIAO et al.	09-2000

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 3-8, 10, 12-13 and 19-24 are rejected under 35 U.S.C. 112, second paragraph. This rejection is set forth in prior Office Action, mailed 05/16/2007.

Claim 1 recites that the HMG-CoA reductase inhibitor is present in amounts "which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient". The specification does not provide a standard for ascertaining the requisite degree of "does not substantially increase…", and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 1, 3-8, 10, 12, 19-22, 30, 32-33 and 38-39 are rejected under 35 USC 102(b) as being anticipated by Liao et al. (WO 00/56403 A1). This rejection is set forth in prior Office Action, mailed 05/16/2007.

Liao teaches the use of HMG-CoA reductase inhibitor such as simvastatin in treating pulmonary arterial hypertension or thromboembolism or increasing blood flow in tissue of a subject alone (page 13, line 19 thru page 14, line 1; page 16, line 2 thru page 17, line 7) or in combination with other active agent such as prostaglandin (page 24, line 16), wherein the simvastatin is administered in 0.01 mg/kg per day to 1000 mg/kg per day (page 20, lines 5-8), more preferably 50-500mg/kg in various dosage forms including oral, rectal, topical, nasal, interdermal or parenteral (page 21, lines 3-11).

With respect to the activity of simvastatin in "in an amount effective to reduce vascular occlusion in the pulmonary arteries of the patient, and which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial

cells of the pulmonary arteries of the patient" (claim 1), "neointimal smooth muscle cell hyperplasia is decreased" (claim 19), "the blood flow is increased by from about 5% to at least about 300%" (claim 21) or "reversing right ventricular hypertrophy" (claim 30), such properties or characteristics deems to be inherent to the referenced method since the administration of same compound (i.e., simvastatin) in overlapping dosage amount inherently possessing therapeutic effect for the same ultimate use as disclosed by the applicant anticipates the claimed invention even absent explicit recitation of underlying mechanism.

Claims 13, 23-34 and 36-37 are rejected under 35 USC 103(a) as being anticipated by Liao et al. (WO 00/56403 A1). This rejection is set forth in prior Office Action, mailed 05/16/2007.

With respect to claims 23-24 and 36-37,

The teaching of Liao has been discussed in above 35 USC 102 (b) rejection.

Liao differs from the claimed invention in various dosage delivery forms including pulmonary, oral, transmucosal, transdermal and parenteral administration, particularly via inhalation administration (e.g., powder inhaler, metered dose inhaler and nebulizer).

However, those of ordinary skill in the art would have been readily optimized effective delivery forms as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate delivery dosage forms for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely

performed by them without undue experimentation, especially in light of the conventional drug delivery forms known in pulmonary hypertension treatment of art.

With respect to claim 13,

The teaching of Liao has been discussed in above 35 USC 102(b) rejection.

The teaching of Liao differs from the claimed invention in the selection of prostacyclin. However, one having ordinary skill in the art would have been motivated to select the claimed compound with the expectation that prostacyclin would not significantly alter the analogous properties of the compound of the reference due to close similarity of the compounds.

(10) Response to Argument

Appellant's arguments and remarks have been carefully considered, but are not deemed to be persuasive.

With respect to the claims rejection of claims 1, 3-8, 10, 12-13 and 19-24 under 35 USC 112, 2nd paragraph,

Appellant in his argument takes the position that the "metes and bounds" of the term "substantially" would be clear to one of skill in the art. Appellant in his argument asserts that the term "which does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient" refers to "an increase of NOS expression or activity to levels which would exist in normal healthy endothelial tissue, but not to any enhancement of NOS expression or activity above levels

that would exist in normal healthy endothelial tissue" at page 10, lines 2 to 6, and one of ordinary skill in the art, reading the specification, could determine normal NOS expression levels in healthy endothelial tissue and would clearly understand what would constitute an enhancement of said expression above that exist in the healthy tissue.

Appellant's argument is not found persuasive. The examiner recognizes that the usage "substantially" may be adequately definite in some cases, but in this situation it is indefinite because it is not further clearly defined. The question is how to ascertain the requisite degree of "an increase of NOS expression or activity to levels which would exist in normal healthy endothelial tissue, but not to any enhancement of NOS expression or activity above levels that would exist in normal healthy endothelial tissue". There is no intrinsic evidence of the specification or extrinsic evidence in which the meaning of words as they would be understood by persons in the field of the invention to "particularly point out and distinctly claim" the invention, 35 USC 112.

Although the specification (Example 5) discloses assay method (e.g., Western immunblotting technique or RT-PCR) in measuring endothelial cell nitric oxidase (eNOS) synthase levels, the specification does not clearly provide a standard for ascertaining the requisite degree of "does not substantially increase", and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is considered that the meaning of the claims should be clear from the wording of the claim alone.

With respect to the rejection of claims 1, 3-8, 10, 12, 19-22, 30, 32-33 and 39 under 35 USC 102(b),

Appellant in his argument takes the position that Liao does not teach the instantly claimed step of administering an amount of a HMG-CoA reductase inhibitor that is effective to reduce vascular occlusion in the pulmonary arteries but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries. Appellant in his argument asserts that the Liao's teaching of a method of increasing endothelial cell nitric oxide synthase activity is actually opposite of what is recited in the Appellant's claims. In appellant's Response filed January 11, 2008, appellant stated:

> Accordingly, an element of the claims is administering an amount of a HMG-CoA reductase inhibitor that is effective to reduce vascular occlusion in the pulmonary arteries but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries. The Appellants contend that Liao does not teach this element. Liao does not teach this element because Liao actually teaches a method for increasing endothelial cell nitric oxide synthase activity. See for instance, page 4, lines 21 to 26, below:
>
> > According to one aspect of the invention, a method is provided for increasing endothelial cell Nitric Oxide Synthase activity in a normocholesterolemic subject who would benefit from increased endothelial cell Nitric Oxide Synthase activity in a tissue. The method involves administering to a normocholesterolemic subject in need of such treatment a HMG-CoA reductase inhibitor that increases endothelial cell Nitric Oxide Synthase activity in an amount effective to increase endothelial cell Nitric Oxide Synthase activity in the tissue of the subject.
>
> The requirement for upregulating eoNOS is reiterated throughout the specification, for example at page 4, lines 23-26; page 6, lines 23-25, page 8, lines 5-7, page 5, lines 9-10, and in the claims, where it is specifically recited in, for example, Claims 1 and 5. It is therefore clear that the cited art intends a dose and route of administration of an HMG-CoA reductase that will result in increased eoNOS activity.
>
> Therefore, because Liao actually teaches a method for increasing endothelial cell nitric oxide synthase activity, it teaches a method opposite of what is recited in the Applicants' claims. Hence, Liao does not teach every element of the rejected claims and, consequently, does not anticipate the claimed invention. For this reason alone, this rejection should be reversed.

Appellant's argument is not found persuasive. Although the Examiner recognizes the Liao's teaching in upregulation of eNOS activity by HMG-CoA reductase inhibitor,

the examiner determines that Liao's "upregulation of eNOS activity" does not refer to plain increase of such activity in an affected cell or tissue, rather "re-establishment of normal base-line levels of eNOS activity" as well as "increasing such activity above normal base-line levels" (page 4, lines 6-8 and page 11, 10, line 32 through page 11, line 16 of WO'403). In other words, the range of upregulation of eNOS activity in Liao includes from range where eNOS activity is increased below normal base-line levels to range where eNOS activity is elevated above normal base-line levels.

The instant Example 5 provides assay method, in vivo, in determining eNOS levels. In the study, the Appellant stated that "the expression of eNOS mRNA...appeared to be significantly lower in diseases rats" (page 33, lines 23-24) and the administration of simvastatin "restored eNOS expression towards the level in normal rats" (page 33, lines 30-31).

Thus, the examiner determines in light of the instant specification (Example 5) that Liao's "upregulation of eNOS activity" falls within the metes and bounds of "does not substantially increase endothelial cell nitric oxidase synthase activity...".

Furthermore, as discussed in the previous O.A. mailed (11/21/06 and 05/16/07), Liao discloses dosage range of "0.01 mg/kg per day to 1000 mg/kg per day", particularly "50-500 mg/kg" (page 20, lines 5-8 of WO'403), which overlaps with the instant dosage range "from about 0.1 to about 100 mg/kg per day" (page 4, lines 27-28 of the instant specification). The administration of same HMG-CoA reductase inhibitor (i.e., simvastatin) in overlapping dosage amount (particularly lower range of limit of Liao compared to the instant dosage) inherently possessing therapeutic effect for the same ultimate use (e.g., pulmonary proliferative vascular disease or pulmonary hypertension)

as disclosed by the Appellant anticipates the claimed invention even absent explicit recitation of underlying mechanism.

Appellant in his argument takes the position that given the disclosure set forth in Liao, one of ordinary skill in the art could not practice the Appellant's claimed invention without undue experimentation. Appellant in his argument asserts that one of ordinary skill in the art could not practice the Appellant's claimed invention without undue experimentation, in view of Liao, because Lao is directed to administering a HMG-CoA reductase inhibitor to unregulated endothelial cell NOS (eNOS) activity and thereby treating a disease condition. In appellant's Response filed January 11, 2008, appellant stated:

> The Appellants' claimed invention is based partially upon the discovery that HMG-CoA reductase inhibitors show efficacy both in (1) preventing the development of smooth muscle cell hyperplasia (including medial hypertrophy), and in (2) inducing apoptosis in diseased and hypertrophied vascular tissues. The Appellants' discovery is in sharp contrast to methods, such as those disclosed in Liao, which teach the administration of HMG-CoA reductase inhibitors to increase expression of ecNOS. As stated in the Appellants' specification at page 10, lines 9 to 24:
>
> > "This discovery is in sharp contrast to earlier ideas postulating that HMG-CoA reductase inhibitors act to increase expression or activity of endothelial cell nitric oxide synthase (NOS), thereby relieving the symptoms of pulmonary hypertension or other vascular disorder by relaxing the vascular smooth muscle cells. Instead, the present applicants show that antiproliferative agents such as HMG-CoA reductase inhibitors are involved in direct resolution of the neointimal smooth muscle hyperplasia and medial hypertrophy that causes the vascular occlusion in disease states associated with lung proliferative vascular disorders. In fact, it is demonstrated herein that antiproliferative agents induce apoptosis of vascular smooth muscle cells, resulting in shrinkage of the tissue and direct resolution of the vascular occlusion. The decrease in vascular occlusion that results is much greater than any vasodilation that could occur from the administration of a vasodilator, even in the presence of normal levels of eNOS."
>
> Accordingly, due to the fact that Liao involves administering a HMG-CoA reductase inhibitor to upregulate endothelial cell NOS activity, the results of which have been questioned[1], and the Applicants' methods involve the administration of a HMG-CoA reductase inhibitor to reverse vascular occlusion by reversing neointimal hyperplasia, and thereby promoting the restoration of normal healthy endothelial cells, the Applicants contend that in view of the teachings of Liao, one of ordinary skill in the art could not practice the claimed invention without undue experimentation. Therefore, for this additional reason Liao et al. is not an appropriate prior art citable under § 102.

Appellant's argument is not found persuasive because the enablement requirement for prior art to anticipate under section 102 does not require utility, unlike the enablement for patents under section 112. Thus, the administration of same compound (i.e., simvastatin) in overlapping dosage amounts (see the instant "from about 0.1 to about 100 mg/kg per day, more preferably from about 0.1 to about 20 mg/kg per day" at page 4, lines 27-28 vs. the referenced "from about 0.01 mg/kg to 1000mg/kg per day…from 50-500mg/kg" at page 20, lines 5-7) inherently possessing therapeutic effect for same ultimate purpose (e.g., treatment of pulmonary hypertension, thromboembolism) as disclosed by the applicant anticipates the claimed invention even absent explicit recitation of underlying mechanism.

Appellant in his argument takes the position that the Liao does not teach the instant method of administering said composition to a patient suffering from a primary pulmonary hypertension. Appellant in his argument asserts that Liao provides the very general range of 0.01 mg/kg to 1000mg/kg as being suitable for administration and there is no evidence that such a dose can be administered to an animal for the purpose of treating primary pulmonary hypertension. In appellant's Response filed January 11, 2008, appellant stated:

> Applicants note that Liao *et al.* does not teach a method wherein this goal can be achieved in a patient suffering from a primary pulmonary hypertension. Liao *et al.* provide the very general range of 0.01 mg/kg to 1000 mg/kg as being suitable for administration. However, the reference fails to provide any evidence that such a dose can be administered to an animal for the purpose of treating primary pulmonary hypertension. The examples provided by Liao *et al.* relate to cell culture assays, for example as illustrated in Figures 1-3, which show changes in ecNOS expression *in vitro*, or to cerebral infarction (Figures 4-6). There is no *in vivo* data provided by Liao *et al.* that would direct one of skill in the art in how to treat primary pulmonary hypertension by administering an HMG-CoA reductase inhibitor in a dose that increases ecNOS activity. While Liao *et al.* speculate and assert that this can be achieved; in fact there is no supporting evidence.
>
> In view of the foregoing discussion and the other deficiencies of Liao *et al.* discussed above, the Applicants contend that Claim 3 is not anticipated by Liao *et al.* because Liao *et al.* fails to teach all the elements of the rejected claims and/or is not enabled with respect to the Applicants' claimed invention. Consequently, the Applicants respectfully request that the 35 U.S.C. § 102(b) rejection be reversed.

Appellant's argument is not found persuasive because proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation. That is, a section 102 prior art reference doe not have be "effective" to be enabling and thus anticipating.

Appellant in his argument takes the position that the there is no mention or teaching of the instant method of reversing right ventricular hypertrophy in a patient suffering from pulmonary hypertension by administering an HMG-CoA reductase inhibitor. Appellant in his argument asserts that before the discovery reported in the instant application, it was highly unexpected that one could achieve an actual reversal of such a serious cardiac disorder. In appellant's Response filed January 11, 2008, appellant stated:

> Applicants respectfully submit that there is no mention or teaching of such a treatment in cited art. Before the discovery reported in the instant application, it was highly unexpected that one could achieve an actual reversal of such a serious cardiac disorder. The cited art is completely silent on the subject, and the deficiencies of the art with respect to pulmonary proliferative diseases are even more noticeable on this point.
>
> Applicants respectfully submit that Liao *et al.* fail to teach the recited elements of the claimed invention. Reversal of the rejection is requested.

Appellant's argument is not found persuasive. As discussed in the preceding comments, in this case, both Liao and the instant application are drawn to the administration of the same compound, HMG-CoA reductase inhibitor (i.e., simvastatin), in overlapping dosage amounts, to the same patient population, for example pulmonary hypertension patient. Thus, the examiner determines that "reversing right ventricular hypertrophy" (as well as "reduce vascular occlusion in the pulmonary arteries of the patient", "neointimal smooth muscle cell hyperplasia is decreased" and/or "blood flow is increase by from about 5% to at least about 300%") deems to be inherent feature present in the referenced method and that Liao anticipates the claimed invention even explicit recitation of underlying mechanism. Anticipation under 35 USC 102 is an essentially irrebuttable question of fact, wherein the court stated that anticipation "cannot be overcome by evidence of unexpected results or teachings away in the art". *In re Malagari, 499 F.2d 1289, 182 USPQ; In re Spada, 911 F.2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990); In re Fracalossi, 681 F.2d 792, 215 USPQ 569 (CCPA 1982); In re Alternpohl, 500 F.2d 1151, 183 USPQ 38 (CCPA 1974); In re Wiggins, 488 F.2d 538, 179 USPQ 421 (CCPA 1973); In re Wilder, 429 F.2d 447, 166 USPQ 545 (CCPA 1970).* Indeed, a reference might reside in a nonanalogous art and yet constitute an anticipation of a claimed invention under 35 USC 102. *In re Self, 571 F.2d 134, 213 USPQ 1 (CCPA 1982).*

With respect to the rejection of claims 13, 23-24 and 36-37 under 35 USC 103(a),

Appellant in his argument takes the position that Liao fails to teach the instant method of treating a lung proliferative disorder wherein the amount of HMG-CoA administered does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient. Appellant in his argument asserts that as the prior art teaches a dosing and regimen that produces an effect opposite of that taught by Appellants, there is not teaching that would suggest or motivate one of skill in the art to pursue Appellant's invention.

Argument in this brief is basically the same as discussed above, so the response discussed above applies here as well and is unpersuasive for reasons just discussed.

Appellant in his argument takes the position that Liao lacks specific guidelines for dose and route of administration whereby one could accomplish the instantly claimed element of claim 23 which requires the administration of an effective dose of a HMG-CoA reductase inhibitor in reducing vascular occlusion in the pulmonary arteries but does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries.

Appellant's Argument in this brief is basically the same as discussed above, so the response discussed above applies here as well and is unpersuasive for reasons just discussed. Especially, similar to Liao (page 22, line 1-2), the instant specification discloses that the determination of pharmaceutical formulations suitable for the instant

invention (e.g., inhalation) are known to those skilled in the art and are described in Remington (see page 22, line found in 5-7). Since there is/are general reference(s) indicating that pharmaceuticals generally may be delivered in various dosage forms including oral, rectal, topical, nasal, interdermal or parenteral, as well as disclosing benefits to be achieved by inhalation or nasal versus other modes of administration, the examiner determines that there exist general art accepted motivations for formulating drugs for inhalation administration. Thus, in absent evidence to the contrary, the examiner maintains that determination of the appropriate delivery dosage forms for treatment involving each of the above mentioned formulation (e.g., inhalation) is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of conventional drug delivery forms known in the pulmonary hypertension treatment art.

Appellant in his argument takes the position that Liao is teaching a method which is exact opposite of the method taught in claim 37 as in Liao's method eNOS activity is increased while in the instant method eNOS activity is not substantially increased.

Argument in this brief is basically the same as discussed above, so the response discussed above applies here as well and is unpersuasive for reasons just discussed.

(11) Related Proceedings Appendix

There are no decisions rendered by a court or the Board in any proceeding identified pursuant to paragraph (c) (1) (ii) of this section.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Brian-Yong Kwon:bk
March 30, 2008

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